



CuCl-catalyzed cycloaddition of 1,3-butadiynes with primary amines: an atom-economic process for synthesis of 1,2,5-trisubstituted pyrroles

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ABSTRACT

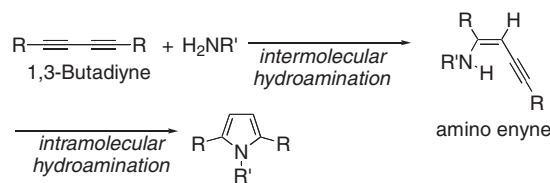
1,3-Butadiynes underwent inter- and intramolecular double hydroamination with primary amines in the presence of CuCl at 100 °C to afford 1,2,5-trisubstituted pyrroles in good to high yields.

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Pyrroles occur in many natural and synthetic compounds possessing interesting physiological and biological activities, and the development of synthetic methodologies for pyrrole derivatives and their transformation is a persistent research topic in organic and pharmaceutical chemistry.¹ A number of new routes to pyrrole derivatives through cycloaddition reactions with the use of alkynes as a reactant have been developed in the last decade.² In addition, Scheme 1 shows an alternative straightforward synthetic route for the formation of 1,2,5-trisubstituted pyrroles from the intramolecular hydroamination of the amino enyne intermediate, which can be formed by selective intermolecular hydroamination of 1,3-butadiyne with the primary amine. This is an attractive method for the synthesis of 1,2,5-trisubstituted pyrroles due to the atom economy and versatility of starting materials. Although CuCl-catalyzed cycloaddition of 1,3-butadiynes with the primary amines at high temperature (140–160 °C) to afford 1,2,5-trisubstituted pyrroles in moderate to good yields was reported,³ with the continuation of our efforts in the development of highly atom-economic approach to carbo- and heterocycles by the cycloaddition reactions using alkynes as reaction partners,⁴ we are interested in the synthesis of a number of 1,2,5-trisubstituted pyrrole derivatives bearing different functional groups by the cycloaddition of 1,3-butadiynes with primary amines under mild reaction conditions.

We initiated our investigation on the reaction of 1,4-diphenyl-1,3-butadiyne (**1a**) with aniline (**2a**) in the presence of copper salts

under different conditions summarized in Table 1. Heating a mixture of **1a** and **2a** (1.0 equiv) in DMF at 100 °C for 24 h in the presence of CuCl (10 mol %) resulted in the formation of 1,2,5-triphenyl pyrrole (**3a**) in 15% GC yield (entry 1). Increasing the amount of **2a** to 5 equiv did not affect the outcome of reaction in the same solvent (entry 2), but the yield of **3a** was slightly increased in DMSO and toluene (entries 3 and 4). Even when the reaction was continued for 72 h, the yield of **3a** could not be improved considerably (entry 5). Since nitrogen ligands have been commonly used as efficient additives to improve the catalytic activity of Cu(I) salts in some organic transformations,⁵ we repeated the same reaction in toluene, this time with the addition of piperidine and pyrrolidine as ligands, and reversibly, deactivation of CuCl was observed (entries 6 and 7). When CuI was used to replace CuCl, a similar result was observed as CuCl was used (entries 8–10). Although further increasing the amount of **2a** (to 10 equiv) could not improve the yield of **3a** in DMF (entry 11), repeating the reaction under solvent-free conditions showed a significantly higher catalytic activity of CuCl to realize the conversion of **1a** in almost

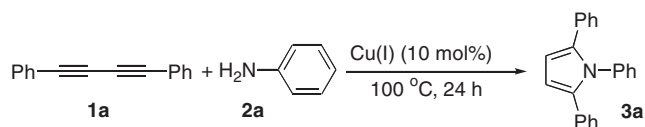


Scheme 1. Atom-economic route for the synthesis of pyrroles.

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Table 1
Copper-catalyzed cycloaddition of 1,4-diphenyl-1,3-diyne (**1a**) with aniline (**2a**)^a



Entry	Catalyst	2a (equiv)	Solvent	Additive (equiv)	GC yield ^b (%)
1	CuCl	1.0	DMF		15
2	CuCl	5.0	DMF		12
3	CuCl	5.0	DMSO		30
4	CuCl	5.0	Toluene		40
5 ^c	CuCl	5.0	Toluene		43
6	CuCl	5.0	Toluene	Piperidine (0.2)	<5
7	CuCl	5.0	Toluene	Pyrrolidine (0.2)	<5
8	CuI	5.0	DMF		10
9	CuI	5.0	DMF	Proline (0.3)	<5
10	CuI	5.0	DMF	2,2'-Bipyridine (0.2)	<5
11	CuCl	10.0	DMF		13
12	CuCl	10.0			>99 (96)
13 ^d	CuCl	10.0			36
14 ^e	CuCl	10.0			11
15	CuCl ₂	10.0			<5
16	Cu(OAc) ₂	10.0			<5

^a Reactions were carried out using 0.5 mmol of **1a** in 2.0 mL of solvent (if used) in a sealed tube at 100 °C for 24 h under nitrogen.

^b Number in parenthesis is isolated yield.

^c 72 h.

^d 5 mol % of CuCl was used.

^e 1 mol % of CuCl was used.

quantitative yield, and **3a** was isolated in 96% yield (entry 12). However, decreasing the amount of CuCl resulted in great decrease of the yield of **3a** (entries 13 and 14). In addition, cupric salts such as CuCl₂ and Cu(OAc)₂ showed no catalytic activity for the present cycloaddition reaction (entries 15 and 16).

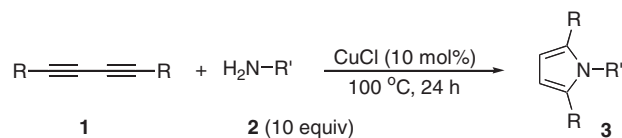
With the optimized conditions indicated in entry 12 of Table 1, we investigated the formation of pyrrole derivatives using a variety of anilines and 1,3-butadiynes as substrates. As summarized in Table 2, a wide range of diversely functionalized anilines, including electron-rich ones such as 4-methylaniline, 4-methoxyaniline, and 3-methylaniline and electron-deficient ones such as monochloro-, dichloro-, and trifluoromethyl substituted anilines, were found to be suitable partners in the undergoing cycloaddition with **1a** to afford the corresponding 1,2,5-triaryl pyrrole derivatives **3b–g** in good to high isolated yields. These results clearly revealed that the electron effect of substituents in anilines could be neglected. Additionally, the relatively low reactivity of *ortho*-substituted anilines such as 2-chloro and 2,3-dichloroaniline compared to *meta*-substituted ones to give pyrrole derivatives **3h** and **3i** in 73% and 72% isolated yields, respectively, is presumably due to the steric hindrance due to the substituent at the *ortho*-position of anilines.

The present catalytic cycloaddition was also applicable to aliphatic amines. For example, the reaction of **1a** with *n*-amylamine (10 equiv) efficiently furnished the corresponding pyrrole derivative **3j** in 85% isolated yields.

Various substituted 1,4-diaryl-1,3-butadiynes bearing either an electron-donating group (*p*-Et, *p*-OMe) or an electron-withdrawing group (3,4-difluoro) readily underwent cycloaddition with **1a**, with the electron-deficient aniline (4-fluoroaniline) and electron-rich aniline (3-methylaniline) to afford high isolated yields of pyrrole derivatives **3l–o**.

The cycloaddition of an unsymmetrical diyne of 1-(2-naphthyl)-4-phenyl-1,3-butadiyne with **1a** gave the expected pyrrole derivative **3p** in 91% isolated yield. In addition, 1,4-bis(2-thienyl)-1,3-

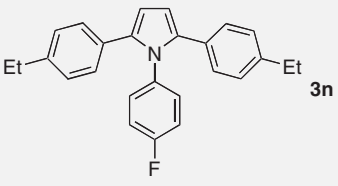
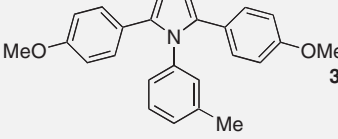
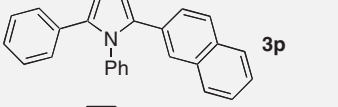
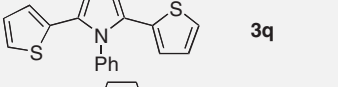
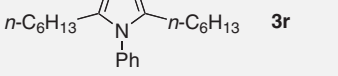
Table 2
Synthesis of 1,2,5-trisubstituted pyrroles by CuCl-catalyzed cycloaddition of 1,3-diyne with amines^a



Pyrrole	Isolated yield (%)
3b	93
3c	95
3d	96
3e	95
3f	92
3g	94
3h	73
3i	72
3j	85
3k	95
3l	92
3m	90

(continued on next page)

Table 2 (continued)

Pyrrole	Isolated yield (%)
	93
	94
	91
	93
	90 (72 h)

^a Reactions were carried out using 1.0 mmol of **1**, 10.0 mmol of **2**, and 0.1 mmol of CuCl in a sealed tube.

butadiyne also underwent the transformation with **1a** to afford a five-membered heterocyclic trimer **3q**, indicating that the coordinative sulfur atom did not affect the catalytic activity of CuCl. **3q** and its analogs are members of an interesting class of organic molecules due to their interesting electrical and/or optical properties.⁶

Furthermore, although the reaction of 1,4-dialkyl-1,3-diyne was sluggish under similar reaction conditions, using a prolonged reaction time could render the desired pyrrole derivatives in satisfactory yields. As an example, the reaction of 7,9-hexadecadiyne with **1a** at 100 °C for 24 h produced the corresponding pyrrole derivative **3r** in only 36% isolated yield, but the use of a longer reaction time (up to 72 h) significantly increased the yield of **3r** to 90% isolated yield.

In conclusion, we have developed an efficient catalytic system for the formation of 1,2,5-trisubstituted pyrrole derivatives by the cycloaddition of 1,4-disubstituted 1,3-butadiynes with various primary amines using CuCl as a catalyst. The noticeable advantages of the present procedure include having easily available starting materials, mild reaction conditions, an inexpensive catalyst, and the high product yields. These qualities make the present catalytic system practical and attractive in the synthesis of pyrrole derivatives.

A typical experimental procedure for the reaction of 1,4-diphenyl-1,3-butadiyne (**1a**) with aniline (**2a**) affording 1,2,5-triphenylpyrrole (**3a**) (Table 1, entry 11): A mixture of 1,4-diphenyl-1,3-butadiyne (**1a**) (202.0 mg, 1.0 mmol), aniline (**2a**) (930.0 mg, 10.0 mmol), and CuCl (9.9 mg, 0.1 mmol) was heated at 100 °C with stirring for 24 h under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, the crude reaction mixture was diluted with CH₂Cl₂ (2.0 mL) and cyclohexane (2.0 mL), and *n*-octadecane (127.0 mg, 0.5 mmol) was then added as an internal

standard for GC analysis. After GC and GC–MS analyses of the reaction mixture, volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography [eluted with CH₂Cl₂/petroleum ether (0:1–1:5)]. **3a** was obtained in 284.4 mg (0.96 mmol, 96%) as a colorless solid. The GC analysis of the reaction mixture disclosed the formation of **3a** in 99.6% GC yield and no **1a** was detectable in the reaction mixture. Data for **3a**: ¹H NMR (300 MHz, CDCl₃) δ 7.25–7.22 (m, 4H), 7.19–7.13 (m, 5H), 7.08–7.02 (m, 6H), 6.48 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 139.1, 135.9, 133.4, 129.1, 128.9, 128.0, 127.4, 126.3, 110.1. GC–MS *m/z* (% rel. int.) 295 (M⁺, 100), 217 (8), 191 (41), 165 (15), 139 (19), 115 (13), 77 (28).

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Supplementary data

Supplementary data (general method, characterization data and charts of ¹H, ¹³C NMR for all products are concluded) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.092.

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